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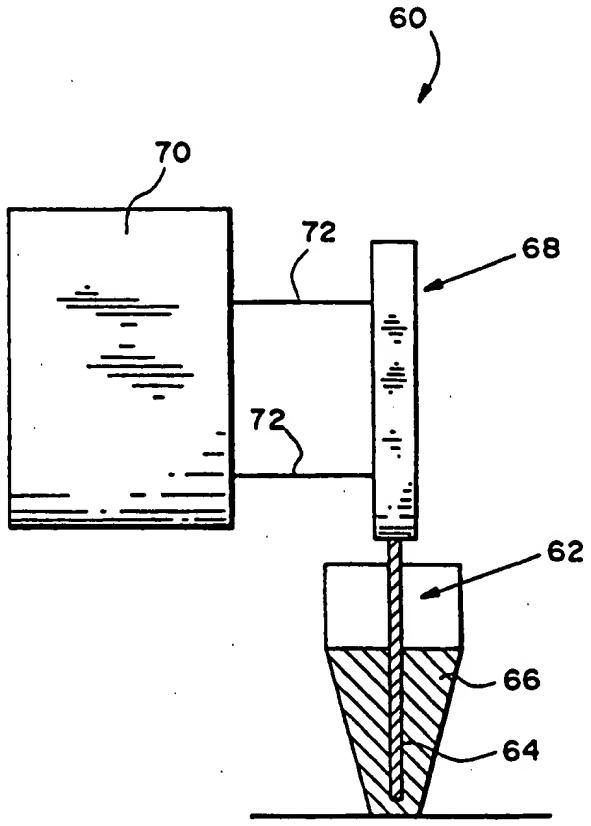
(57) Abstract

Methods and devices for application of ultrasound to a small area of skin for enhancing transdermal transport. An ultrasound beam having a first focal diameter is channelled into a beam having a second, smaller diameter without substantial loss of energy. Higher energy ultrasound can be used while causing less pain. Alternatively, ultrasound energy is applied through a vibrating element positioned just contacting, above or extending into the skin. Use of the element facilitates extraction of analyte and may enhance drug delivery. A two step noninvasive method involves application of ultrasound to increase skin permeability and removal of ultrasound followed by transdermal transport that can be further enhanced using a physical enhancer.



ULTRASOUND ENHANCEMENT OF TRANSDERMAL TRANSPORT

This application claims priority from U.S. provisional patent application serial numbers 60/020,953 filed June 28, 1996, 60/022,925 filed August 1, 1996, 60/022,923 filed August 1, 1996, 60/023,636 filed August 9, 1996, 60/034,657 filed January 8, 1997, 60/024,639 filed August 22, 1996, a U.S. provisional patent application filed December 11, 1996 as Express Mail No. EH446654019US entitled Transdermal Extraction and Measurement of Blood or Interstitial Fluid Analytes Using a Vibrating Element With an Integrated Sensing System", and a U.S. provisional patent application filed January 3, 1997 as Express Mail No. EH618852288US entitled "A Device for Painless Extraction of Blood or Interstitial Fluid for Blood Analyte Measurement".

Background of the Invention

The present invention generally relates to improved methods and devices for transdermal transport using ultrasound. More specifically, methods and devices are provided to channel or focus an ultrasound beam so that it is applied to a small area of skin and can enhance drug delivery and analyte collection. Methods and devices are provided to localize the ultrasound energy onto a vibrating element which applies the ultrasound energy to a small area of the skin.

Drugs are routinely administered orally or by injection. The effectiveness of most drugs relies on achieving a certain concentration in the bloodstream. Many drugs exhibit undesirable behaviors that are specifically related to a particular route of administration. For example, drugs may be degraded in the gastrointestinal (GI) tract by the low gastric pH, local enzymes, or interaction with food or drink in the stomach. The drug or disease itself may forestall or compromise drug absorption because of vomiting or diarrhea. If a drug entity survives its trip through

applications because of the low skin permeability to drugs. This low permeability is attributed to the stratum corneum (SC), the outermost skin layer which consists of flat, dead cells filled with keratin fibers (keratinocytes) surrounded by lipid bilayers. The highly-ordered structure of the lipid bilayers confers an impermeable character to the SC (Flynn, G. L., in *Percutaneous Absorption: Mechanisms-Methodology-Drug Delivery.;* Bronaugh, R. L., Maibach, H. I. (Ed), pages 27-53, Marcel Dekker, New York, 1989). Several methods have been proposed to enhance transdermal drug transport, including the use of chemical enhancers, i.e. the use of chemicals to either modify the skin structure or to increase the drug concentration in a transdermal patch (Burnette, R. R., in *Developmental Issues and Research Initiatives*; Hadgraft J., G., R. H., Eds., Marcel Dekker: 1989; pp. 247-288; Junginger, et al. in *Drug Permeation Enhancement*; Hsieh, D.S., Eds., pp. 59-90; Marcel Dekker, Inc. New York 1994) and the use of applications of electric fields to create transient transport pathways [electroporation] or to increase the mobility of charged drugs through the skin [iontophoresis] (Prausnitz *Proc. Natl. Acad. Sci. USA* 90, 10504-10508 (1993); Walters, K. A., in *Transdermal Drug Delivery: Developmental Issues and Research Initiatives,* Ed. Hadgraft J., Guy, R.H., Marcel Dekker, 1989). Another approach that has been explored is the application of ultrasound [sonophoresis].

Ultrasound has been shown to enhance transdermal transport of low-molecular weight drugs (molecular weight less than 500) across human skin, a phenomenon referred to as sonophoresis (Levy, J. Clin. Invest. 1989, 83, 2974-2078; Kost and Langer in *"Topical Drug Bioavailability, Bioequivalence, and Penetration"*; pp. 91-103, Shah V. P., M.H.I., Eds. (Plenum: New York, 1993); Frideman, R. M., *"Interferons: A Primer"*, Academic Press, New York, 1981). Although a variety of ultrasound conditions have been used for sonophoresis, the most commonly used conditions correspond to therapeutic ultrasound (frequency in the range of between one MHz and three MHz, and

measurements. Other groups have used a laser to breach the integrity of the stratum corneum and thereby make it possible for blood or interstitial fluid to diffuse out of such a hole or to be obtained through such a hole using pneumatic force (suction) or other techniques. An example of such a laser based sampling device is disclosed in US Patent No. 5,165,418 to Tankovich and WPI ACC No: 94-167045/20 by Budnik (assigned to Venisect, Inc.).

A problem with methods that penetrate the skin to obtain interstitial fluid is that interstitial fluid occurs in the body in a gel like form with little free fluid and in fact there is even negative pressure that limits the amount of free interstitial fluid that can be obtained. When a very small hole is made in the skin, penetrating to a depth such that interstitial fluid is available, it takes a great deal of mechanical force (milking, vacuum, or other force) to obtain the quantity of blood used in a glucose meter.

It would be of significant utility to be able to obtain a sample of blood or interstitial fluid more quickly, using an easier procedure, and noninvasively.

Summary of the Invention

The methods and devices described herein channel or focus an ultrasound beam onto a small area of skin. In some embodiments, methods and devices utilizing a chamber and ultrasound probe disclosed herein can be used to noninvasively extract analyte and deliver drugs. This provides many advantages, including the ability to create a small puncture or localized erosion of the skin tissue, without a large degree of concomitant pain. The number of pain receptors within the ultrasound application site decreases as the application area decreases. Thus, the application of ultrasound to a very small area will produce less sensation and will allow ultrasound and/or its local effects to be administered at higher intensities with little pain or discomfort. Channeling of ultrasound geometrically is one way to apply ultrasound to a small area. The

Figure 6 is a side elevational view of a fourth embodiment of an ultrasound channeling chamber having an array of transducers arranged hemi-spherically.

Figure 7 is a side elevational view of a device for application of ultrasound through a vibrating element.

Figure 8 is a side elevational view of a device for application of ultrasound through a vibrating element incorporated with a sensor for sensing an analyte.

Figure 9 is a side elevational view of another device for application of ultrasound through a vibrating element.

Figure 10 is a side elevational view of a device for application of ultrasound through a plurality of vibrating elements.

Figure 11 is a perspective view of a noninvasive ultrasound application device.

Detailed Description of the Invention

Ultrasound is defined as sound at a frequency of higher than about 20 kHz and 10 MHz, with intensities of between greater than zero and three W/cm^2. Ultrasound is preferably administered at frequencies of less than or equal to about 2.5 MHz to induce cavitation of the skin to enhance transport. Exposures are typically for between 20 seconds and 10 minutes, continuously, but may be shorter and/or pulsed. It should be understood that although the normal lower range of ultrasound is 20 kHz, one could achieve comparable results by varying the frequency to less than 20 kHz, that is, into the sound region down to about one kHz. The intensity should not be so high as to raise the skin temperature more than about one to two degrees Centigrade.

As used herein, sonophoresis is the application of ultrasound to the skin. "Low frequency" sonophoresis is ultrasound at a frequency that is less than one MHz, more typically in the range of 20 to 100 kHz, which is applied continuously or, preferably, in pulses, for example, 100 to 500

antivirals, antifungals, antibiotics, local anesthetics, and saccharides and polysaccharides, can also be administered. The drug will typically be administered in an appropriate pharmaceutically acceptable carrier having an absorption coefficient similar to water, such as an aqueous gel, ointment, lotion, or suspension. Alternatively, a transdermal patch can be used as a carrier.

A variety of analytes are routinely measured in the blood, interstitial fluid and/or lymph. Examples of typical analytes that can be measured include blood sugar (glucose), cholesterol, bilirubin, creatine, vitamin K or other clotting factors, uric acid, carcinoembryonic antigen or other tumor antigens, and various reproductive hormones such as those associated with ovulation or pregnancy.

The methods and devices disclosed herein may achieve greater transdermal transport by inducing cavitation either inside or outside of the skin. Cavitation is the growth and oscillations of air bubbles present in fluids and air pockets present in the keratinocytes of the SC. Application of low-frequency ultrasound appears to induce cavitation inside as well as outside the skin and disorganize the SC lipid bilayers thereby enhancing transdermal transport. In addition, oscillations of cavitation bubbles may result in significant water penetration into the disordered lipid regions and may cause the formation of aqueous channels through the intercellular lipids of the SC. This allows transport of permeants across the disordered lipid domains, then across keratinocytes and the entire SC. This transport pathway may result in an enhanced transdermal transport as compared to passive transport because the diffusion coefficients of permeants through water, which is likely to primarily occupy the channels generated by ultrasound, are up to 1000-fold higher than those through the ordered lipid bilayers, and the transport path length of these aqueous channels may be much shorter (by a factor of up to 25) than that through the tortuous intercellular lipids in the case of passive transport.

Ultrasound Channeling or Focusing

absorbs acoustic energy such as plexiglass or other non-deforming material such as metal, are shaped to define a cavity 28 having the shape of a truncated cone with a large opening and a small opening. The cavity is preferably filled with a coupling medium 30 which transmits ultrasound, preferably transmitting sound in a manner equivalent to or better than air. The interior surface of the walls facing the cavity may be lined with an ultrasound reflecting medium such as a metal, polymer, or ceramic material. Metals such as aluminum may be preferred due to their high heat conductivity which may minimize temperature increase upon ultrasound application. An adhesive layer 32 on the bottom of the chamber is used to attach the chamber to the skin 34.

A second embodiment of a chamber is illustrated in Figure 3. In this embodiment, the interior walls 40 define a cavity 42 that is horn shaped, wherein the larger opening is towards the transducer 44 and the smaller opening is towards the skin 46. The chamber is optionally connected to a vacuum pump through a port 48 which opens into the coupling medium 50. Figure 4 illustrates another optional aspect of the chambers, wherein the chamber optionally includes a pair of electrodes 52 for application of electric current to the skin as an additional mechanism for transport enhancement. The necessary current is provided by a current generator (see Figure 1).

The Transducer

The ultrasound transducer is located at the larger end of the cone or the horn. The transducer may be either a piezo, ceramic or polymer block. The transducer may be machined from a single block of appropriate material or may be built by gluing multiple sheets of corresponding material. The focal diameter of the ultrasound beam before it is channeled may be between several millimeters to several centimeters. Ultrasound energy is localized at the small opening of the chamber due to channeling of the ultrasound beam. The second diameter of the beam is between about one μm to two cm, preferably between about 0.1 mm to one cm. The acoustic energy should not decrease more

Figures 5 and 6 may also include vacuum means and means to apply electric current or other physical enhancers.

Coupling Medium

The cavity may be filled with an aqueous or non-aqueous coupling medium including, but not limited to, water, saline, alcohols including ethanol and isopropanol (in a concentration range of 10 to 100% in aqueous solution), surfactants such as Triton X-100 or Sodium Dodecyl Sulfate (preferably in a concentration range of between 0.001 and 10% in aqueous solution), DMSO (preferably in a concentration range of between 10 and 100% in aqueous solution), fatty acids such as linoleic acid (preferably in a concentration range of between 0.1 and two% in ethanol-water (50:50) mixture), azone (preferably in a concentration range of between 0.1 and 10% in ethanol-water (50:50) mixture), polyethylene glycol in a concentration range of preferably between 0.1 and 50% in aqueous solution, histamine in a concentration range of preferably between 0.1 and 100 mg/ml in aqueous solution, EDTA in a concentration range of preferably between one and 100 mM, sodium hydroxide in a concentration range of preferably between one and 100 mM, and combinations thereof.

In the case of drug delivery, the coupling medium also contains a drug that is transported across the skin by diffusion or other driving forces including convection and iontophoresis.

The coupling medium increases the efficient transfer of ultrasound energy from transducer to the skin. Appropriate mixtures of these coupling media may also enhance cavitation activity near the skin or inside the skin, increasing effectiveness of transport of molecules across the skin. Experiments have shown that cavitation can be affected by the coupling medium. Physico-chemical attributes of the medium such as vapor pressure and surface tension influence the degree of cavitation of the medium. Cavitation can also be enhanced by providing nuclei in the form of gas bubbles, crevices, or particulates such as titanium dioxide particles or polymer particles.

fluid. If the element is just touching or penetrates the skin, coupling medium is not necessary.

Another advantage of using coupling media is that acoustic streaming may result. The application of ultrasound in fluids is known to produce convective flow, a condition termed acoustic streaming. Streaming velocities are highest near the ultrasound source. This streaming can alter biological tissue, causing cell distortion and lysis or producing convective flow patterns inside tissue and cells. When acoustic streaming occurs over an existing hole in the skin, drug delivery can be facilitated by the convective flow of drug-containing fluid into the hole or the extraction of clinically relevant analytes can be facilitated through the convective flow of interstitial fluid or blood out of the hole.

Moreover, cavitation, mechanical oscillations of the skin, and local shearing forces may be increased using an appropriate coupling medium and may further enhance transdermal transport.

The pain receptors of the skin are present in the dermis but not the outermost layers of the skin, the epidermis and stratum corneum. Thus the epidermis and stratum corneum may be penetrated or small areas removed with little or no sensation. The outer layers of skin can be abraded through the use of a vibrating element, causing a break in the skin integrity. Alternatively, a needle penetrating only the outer most layers of the skin can create a very small hole (from about 50 μm to one mm in diameter) through which blood or interstitial fluid can be collected from the dermis without pain. The element can also produce acoustic streaming which may enhance the flow of fluid from the hole, resulting in the collection of fluid volumes which are practical for analysis. The enhanced fluid flow allows the extraction of blood from sites that are less vascularized and less innervated than the finger tips, such as, for example, the wrist or forearm. Thus a measurement can be taken at a site where pain is much less likely to occur as well as from a fingertip without pain.

large displacements such as Bimorph transducers and stacked piezoelectric transducers are preferred. Vibrations produced by the transducer 68 are translated to the element which oscillates, preferably in the transverse mode.

Oscillations are produced using an alternating voltage generator coupled to a power amplifier. The voltage wave form is preferably sinusoidal. The ultrasound producing system consisting of the element, transducer, voltage generator and power amplifier, may be powered by standard household power or through a battery. The ultrasound transducer 68 is connected to electrical signal generator and amplifier 70 through electrical contacts 72.

The vibrating element may be fabricated with a channel in the center to provide means for collection of the blood or interstitial fluid or delivery of drug. Alternatively, the analyte may be collected, or the drug delivered from, the chamber.

Figure 9 illustrates an embodiment of a device 110 for application of ultrasound through a vibrating element that is positioned just touching the skin surface or that penetrates the skin. A shaft 112 is connected to vibration producing means (not shown) located in enclosure 114. The vibration producing means may operate by mechanical, electrical, electromechanical, or ultrasonic means. Vibration of the element may be transverse, that is, perpendicular to the skin, parallel to the skin, or at an angle. The device 110 is operated by a rechargeable battery and operated by means of switch 116. The vibration frequency applied to the element varies from about 1 kHz to 100 kHz. The magnitude of vibration of the shaft varies from about one μm to five mm.

Shaft 112 is connected to element holder 118 which retains element 120 and may lock element 120 in place. Element 120 may be a needle. Cap 122, optionally including capillary tube 124, has a hole through which element 120 protrudes. The diameter of the hole varies from about 10 μm to five mm and determines the magnitude of vibration of the element tip. The length of the element protruding may be

The element can be of any practical length and from between about 10 μm and two cm, preferably between about 100μm to 500 μm in diameter.

The distance of the vibrating element into or from the skin is important to create a small hole or abrasion in the skin and generate adequate acoustic streaming, if coupling media is not used. The unit may possess a subunit for controlling the distance of the element from the skin at between about 0.1 and 5 mm or the depth of the vibrating element into the skin in the range of up to about 150 μm. The subunit may alternatively position the element to where it touches the skin and impresses the skin without puncturing the skin. The element may puncture the skin after it begins to oscillate. The unit may also possess a subunit, which may be the same subunit, to control the downward force the needle exerts on the skin. This depth and/or force controlling subunit may be a cantilever beam on which the transducer and vibrating element are fixed.

It is preferred, to maximize oscillations at the tip of the element, to have the length of the element equal to odd multiples of the ultrasound wavelength divided by four. The deflection at the tip can also be modified by changing the stiffness of the element, with stiffer materials such as tungsten or 304 stainless steel resulting in smaller deflections than a more flexible material such as copper or music wire. The geometry of the tip of the element can be modified to produce different forces and flow patterns near the surface of the skin. A pointed tip will result in highly localized shearing forces and acoustic streaming near it while a blunt tip will produce more dispersed forces. These forces, and thus transdermal transport enhancement, can also be distributed by using arrays of elements mounted on transducer(s). The vibrating element is located near the skin hole to maximize the pumping action of acoustic streaming.

The element may be driven at a frequency in the range of between one kHz and 100 kHz, preferably between about 5 kHz and 100 kHz,

the needle from penetrating too deeply into the skin when the device is placed upon the skin.

The vibrating element 76 is fabricated with a channel in its center to provide space for the collection of blood or interstitial fluid. The channel may be lined with a coating such as borosilicate glass or silicon dioxide to facilitate the capillary flow of fluid. The vibrating element with integrated channel may be produced by silicon micromachining.

The system operates by fastening the disposable unit 80 to the transducer 82 and placing the housing 98 against the skin 88. The system is then activated and the extracted fluid is transferred through the element's channel to the sensor. The analyte of interest is measured and the reading displayed to the user. The system is automatically deactivated and the user discards the disposable unit.

The sensing system may be in direct contact with the coupling media or the coupling media may be transferred to the sensor. Transfer may occur by wicking with an absorbent material, by capillary action, by electroosmotic flow, or by pumping including ultrasound pumping.

The unit can be constructed to function as a closed loop drug delivery unit, including drug delivery means, analyte recovery means, sensing means to measure the analyte, and control means to provide a signal to the drug delivery means. In a preferred embodiment, the unit would include subunits to withdraw fluid and calculate the concentration of glucose therewithin, determine the amount of insulin needed, and deliver that amount of insulin.

Another noninvasive technique, illustrated by Figure 11, is useful for analyte extraction. The technique is described as an exemplary embodiment but it should be realized that many changes can be made from the parameters and device described herein. The technique employs a chamber 140 and an ultrasound probe 142. The chamber may have a variety of shapes but is cylindrical in the exemplary embodiment, with open ends, about 1.5 cm^2 in area. One open end of the chamber is placed against the skin 144 at the desired location. Saline (about one ml) may be

hour were obtained and blood glucose levels of 100 mg/dl. These fluxes are 70 times higher than those obtained using reverse iontophoresis.

Other transport enhancement methods could be used instead of, or in addition to, vacuum. For example, other transdermal transport driving forces include osmotic pressure gradient, electric current, ultrasound under different conditions, electroporation, magnetic fields, and mechanical pressure.

This two step method could be used as well for drug delivery. The skin would be made permeable by application of ultrasound followed by the application of drug to the skin and transport of the drug either by diffusion or with the help of a physical enhancer.

Practical Application

Practical operation of a sonophoretic analyte monitoring device is conceived as follows. The patient unpacks a disposable unit and inserts it into a portable or bench-top ultrasound generator. The ultrasound generator may also include circuitry for skin resistance or hemoglobin measurements, analyte concentration measurements, and display of the measured analyte concentration. The entire system (sonicator and disposable unit) is placed against the skin and ultrasound is activated for a certain period of time either alone or along with other physico-chemical fields including chemicals, electric field, vacuum, and pressure fields. The extracted analytes from the skin are collected in the disposable unit and are measured using appropriate assays. A similar operation may be used for drug delivery where the patient unpacks a disposable containing drug and loads it into an ultrasound generating device. The entire assembly is placed against the skin and the device is activated.

Alternatively, the sensing element could be located elsewhere and the contents of the chamber in contact with skin and exposed to ultrasound can be pumped using mechanical forces, capillary forces, ultrasound, vacuum, or electroosmotic forces into the sensing chamber and analyzed for the analyte of interest.

through the chamber through two windows. The window through which the light passes may be separate from the ultrasound transducer or the beam may pass directly through the transducer.

In other words, the analyte sensing system may consist of enzymes that react with the analyte of interest and either electrochemical or optical transducers that measure the content of reaction. Examples of such enzymes include but are not limited to glucose oxidase and glucose dehydrogenase. Using glucose oxidase as an example, glucose is measured using either of the following reactions: glucose+0_2 ⇒ gluconolactone+H_20_2; glucose+$2M_o$ ⇒ gluconolactone+$2M_R$ where M is a mediator in its oxidized (O) or reduced (R) state. An electrochemical transducer then measures either the consumption of 0_2, M_o or the production of H_20_2 or M_R. Examples of mediators (M) include, but are not limited to, ferrocene and its derivatives or polymers containing Os (bis-bipyridine)$_2$Cl. The electrochemical transducer may consist of a two or three electrode system, with the electrode materials being gold, silver, silver/silver chloride, platinum, palladium or carbon. Electrode potentials are controlled by and electrochemical reactions monitored by a potentiostat.

Optical transducers monitor the disappearance of M_o or the appearance of M_R. The optical transducer consists of a light source which may be mono- or polychromatic and may be a light-emitting diode or an optical fiber. In addition to the light source, the optical transducer contains a device to measure the transmittance or absorbance change produced by the enzymatic reaction. This device may be, but is not limited to, a photodiode.

The chamber may also contain mechanisms for measuring concentrations of more than one analyte for the purpose of minimizing variability in fluxes of extracted analytes. For example, measurement of the amount of ions extracted during sonophoresis could be used as a normalization factor for the variations in the amount of glucose extracted during the same period of time. This may be achieved by measuring conductivity in the

of a patient, as follows. A typical diabetic patient (70 Kg weight) takes about 12 Units of insulin three times a day (total dose of about 36 Units per day: cited in 'World Book of Diabetes in Practice' Krall, L.P. (Ed), Elsvier, 1988). If each insulin dose was to be delivered by sonophoresis in one hour, the required transdermal flux would be 12 U/hour. Note that one unit (one U) of insulin corresponds approximately to 40 mg of insulin. The transdermal patch area used in these calculations is 40 cm^2 (the area of a transdermal Fentanyl™ patch [ALZA Corporation]). The donor concentrations used in these calculations are 100 U/ml in the case of insulin (commercially available insulin solution [Humulin™]), 3 $x10^7$ in the case of γ-interferon (typical concentration of interferon solution recommended by Genzyme Corporation), and 3 $x10^5$ U/ml in the case of erythropoeitin [Davis J., Arakawa T., Strickland T., Yphantis D., Biochemistry, 2633-2638, 1987].

A typical γ-interferon dose given each time to patients suffering from cancer or viral infections is about 5 $x10^6$ U (Grups J. W., Frohmuller H. G., Br. J. Med., 1989, 64 (3) 218-220; Parkin J. M., Eales L., Galazka A., Pinching A., Br. Med. J., 1987, 294: 1185-1186) Similar doses of α-interferon and β-interferon have also been shown to enhance the immune response of patients suffering from viral infections and cancer (cited in 'Clinical Applications of interferons and their inducers', Ed. Stringfellow D., Marcel Dekker, New York, 1986). If this interferon dose was to be given by sonophoresis in one hour, the required transdermal flux would be 5 $x10^6$ U/hour. Note that one unit of γ-interferon corresponds approximately to one pg of γ-interferon.

A typical daily erythropoeitin dose given subcutaneously to anemic patients is about 400 U (cited in 'Subcutaneous Erythropoeitin, Bommer J., Ritz E., Weinreich T., Bommer G., Ziegler T., Lancet, 406, 1988). If this dose was to be delivered in three steps, each involving sonophoresis for one hour, the transdermal flux required would be about 140 U/hour. Note that one unit of erythropoeitin corresponds approximately to 7.6 nanograms of erythropoeitin.

volunteers with 5 repetitions at the same site. The results are summarized in Table 1.

Table 1. Transdermal Glucose Extraction from Human Volunteers: Glucose Concentration (μg/ml) in Extraction Fluid

Extract Number	Subject 1 Site 1	Subject 1 Site 2	Subject 2 Site 1	Subject 2 Site 2	Subject 3 Site 1	Subject 4 Site 1
1	2.4	1.4	1.8	1.1	3.5	0.62
2	1.5	0.89	1.1	1.8	2.3	0.57
3	—	1.0	1.2	1.2	2.5	0.40
4	0.74	0.86	0.97	2.9	1.9	0.45
5	1.8	0.72	1.6	1.7	2.9	0.56
Average	1.6	0.97	1.3	1.74	2.6	0.52
RSD	43%	25%	15%	43%	22%	17%

The amounts of glucose recovered and the standard deviation between the same subject are comparable to results obtained using reverse iontophoresis. However, the presently disclosed method took less time by a factor of 15.

Example Two: Extraction of Glucose with Vibrating Needle Element.

In this case the same general approach was used, but in addition there was a mechanism to use the ultrasound element to puncture the skin, then it was removed and vibrated in the transverse mode to pump out more glucose than could be otherwise obtained. To demonstrate this concept, a sewing needle was used as the transverse oscillating element. The chamber shown in Figure 7 was placed against the skin. The system was set up such that the oscillating needle could be lowered independent of the chamber. A micrometer was used to advance the needle until it penetrated the stratum corneum into the epidermis or further penetrated to the dermis, to extract interstitial fluid or blood, respectively. Then the

The oscillating needle was lowered to be at the bottom of the sample well, as indicated by moving a finger under the well and seeing the needle move. By adjusting a lab clamp holding the sample well, the well was lowered the minimum amount such that the needle no longer moved when a fingertip was moved under the bottom of the sample well.

The back of the left hand was positioned in touch with the bottom of the well so fluid would not leak out. 20 microliters of distilled water were put in the well and the sample was sonicated for one minute, continuous power, at an amplitude of about 35%-36%. The sample was retrieved using another 40 microliters to wash out sample well and the samples were assayed using a standard HPLC procedure.

The results showed concentrations of glucose were obtained comparable to those obtained with Example 1. The average concentration obtained from five volunteers was 1.65μ g per ml. The average standard deviation was 1.16.

In another aspect, the devices and methods disclosed herein could utilize sound or ultrasound produced according to a phenomenon known as "Tartini tones", first described by Giuseppe Tartini, an 18th century Italian composer and described in an article by Larry Armstrong in the December 2, 1996 issue of Business Week, pages 108-109. Lower frequencies (less than 10 kHz) can be produced using much smaller transducers. The method relies on the phenomenon that when two sound or ultrasound waves having different frequencies interact, a third wave is created, having a frequency intermediate between the two. The third wave can be focused.

10. A device for application to the skin for enhancing transdermal transport, comprising:

an ultrasound transducer geometrically configured to direct an ultrasound beam of about 20 kHz to 200 kHz to an area on the skin about 100 μm to one cm in diameter; and

a cavity between the transducer and the skin containing a coupling medium.

11. The device of claim 10, wherein the transducer is hemispherical in shape.

12. The device of claim 10, wherein the transducer comprises a plurality of transducers arranged in a hemisphere.

13. A method of enhancing transdermal transport, comprising the steps:

providing an ultrasound beam having a frequency from about 20 kHz to 2 MHz and a first diameter;

geometrically channeling the ultrasound beam to a second diameter of between about 100μm and one cm that is smaller than the first diameter wherein the energy of the beam does not decrease more than about 50%; and

applying the channeled beam to an area of skin.

14. A device for enhancing transdermal transport, comprising:

a transducer producing energy at a frequency between about 1 kHz and 100 kHz; and

at least one element arranged to receive energy from the transducer and transmit vibrations to the skin.

15. The device of claim 14, further comprising a housing containing the element so that the at least one element extends into the skin up to about 150 μm when the housing is placed against the skin.

16. The device of claim 14, further comprising a housing containing the element so that the at least one element just contacts the skin when the housing is placed against the skin.

27. The method of claim 24, further comprising the step of providing a coupling medium in contact with the element and the skin and wherein the element is positioned so that it does not contact the skin and wherein the element causes cavitation sufficient to increase permeability of the skin.

28. The method of claim 24, further comprising the step of creating a hole in the skin through which analyte can be extracted.

29. The method of claim 28, wherein the hole is created by the element.

30. The method of claim 24, wherein the element vibrates in the transverse mode.

31. A method of effecting transdermal transport, comprising the steps:

applying ultrasound to an area of skin to make the skin more permeable;

removing the ultrasound; and

applying a transdermal transport driving force selected from the group consisting of additional ultrasound, suction, osmotic pressure gradient, iontophoresis, electroporation, magnetic field and mechanical pressure.

add concentration gradient ?,

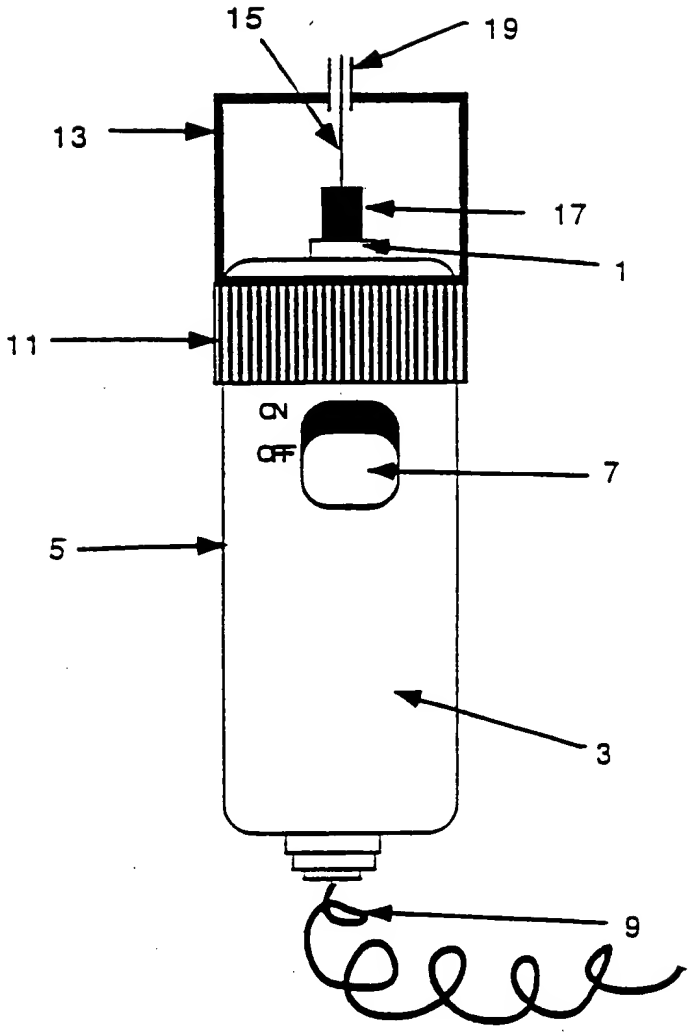


Figure 1

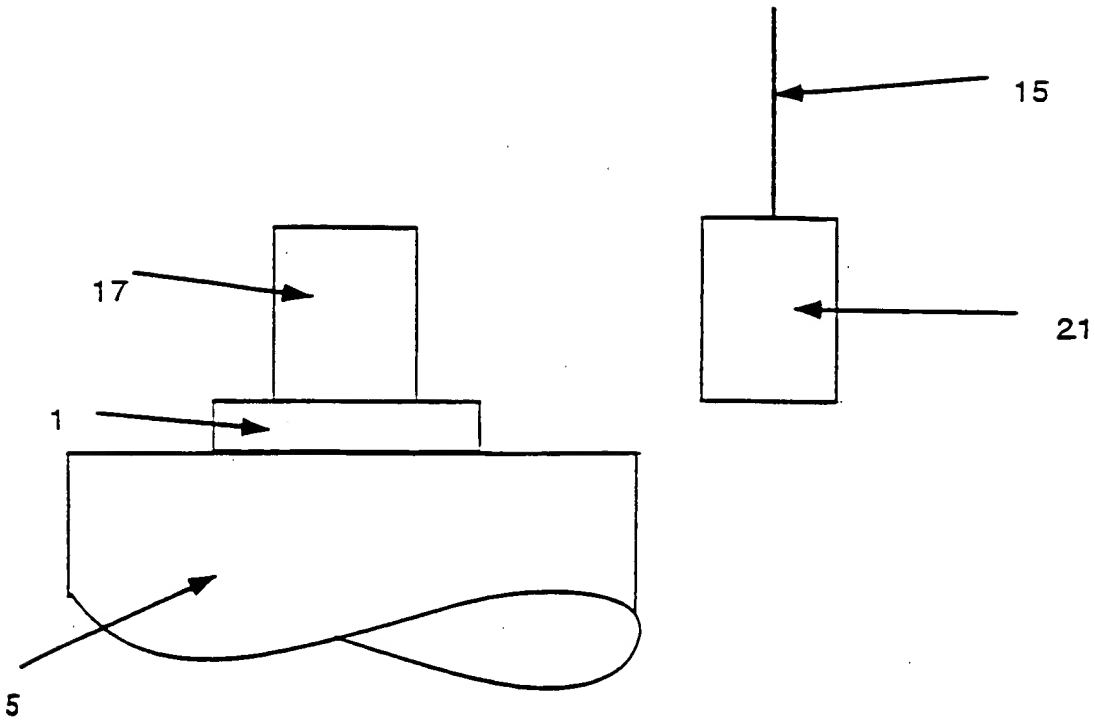


Figure 2

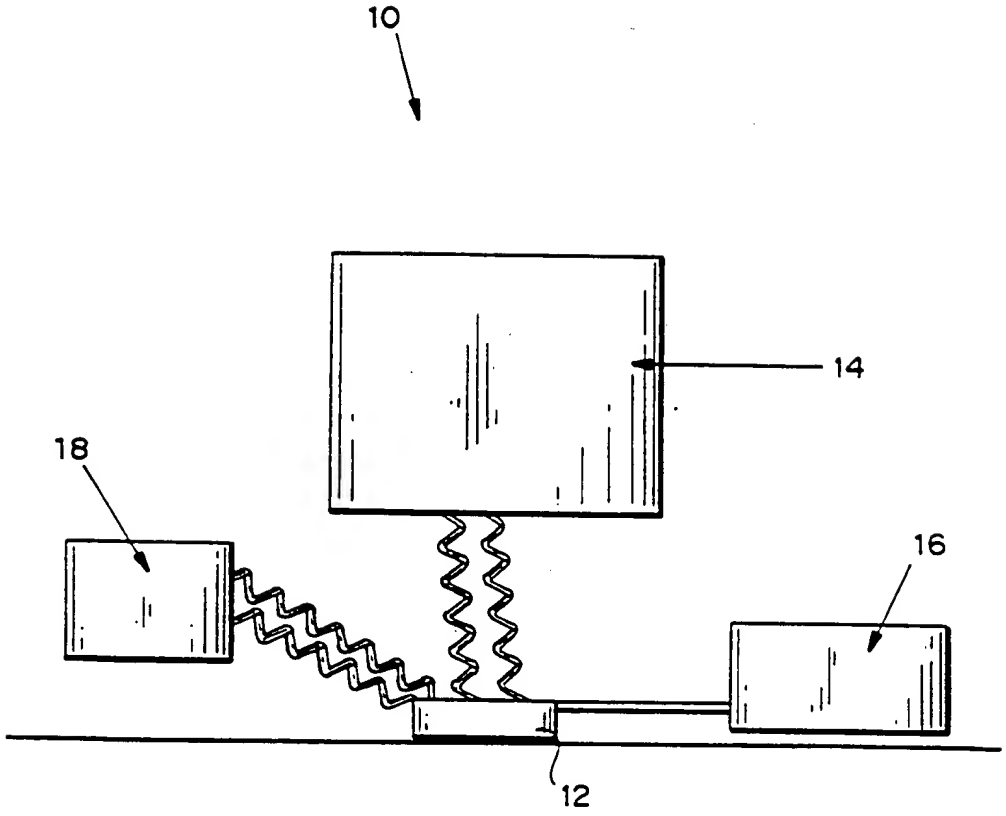


FIG. 1

FIG. 2

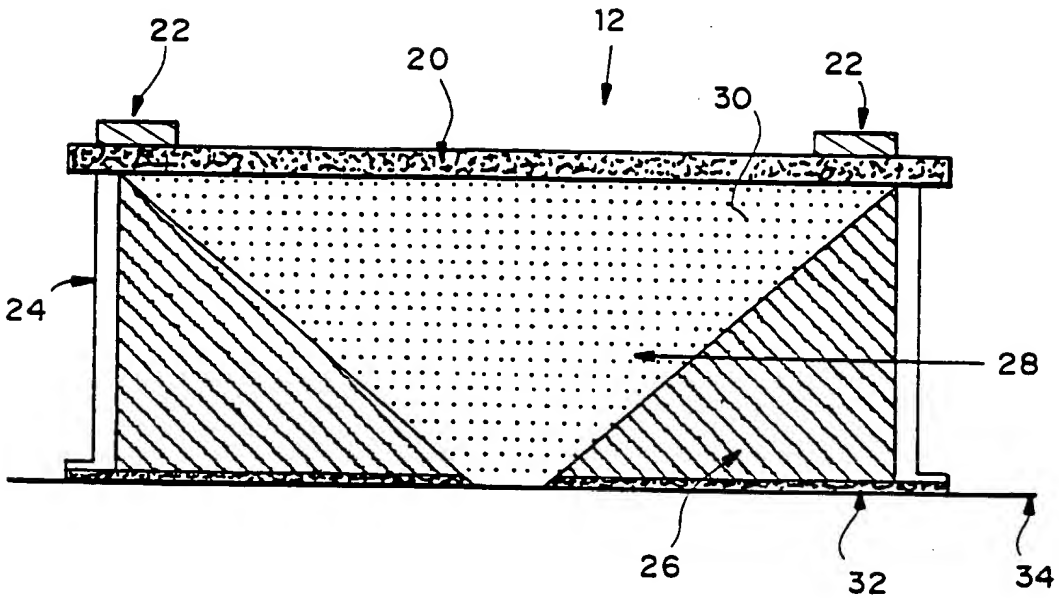
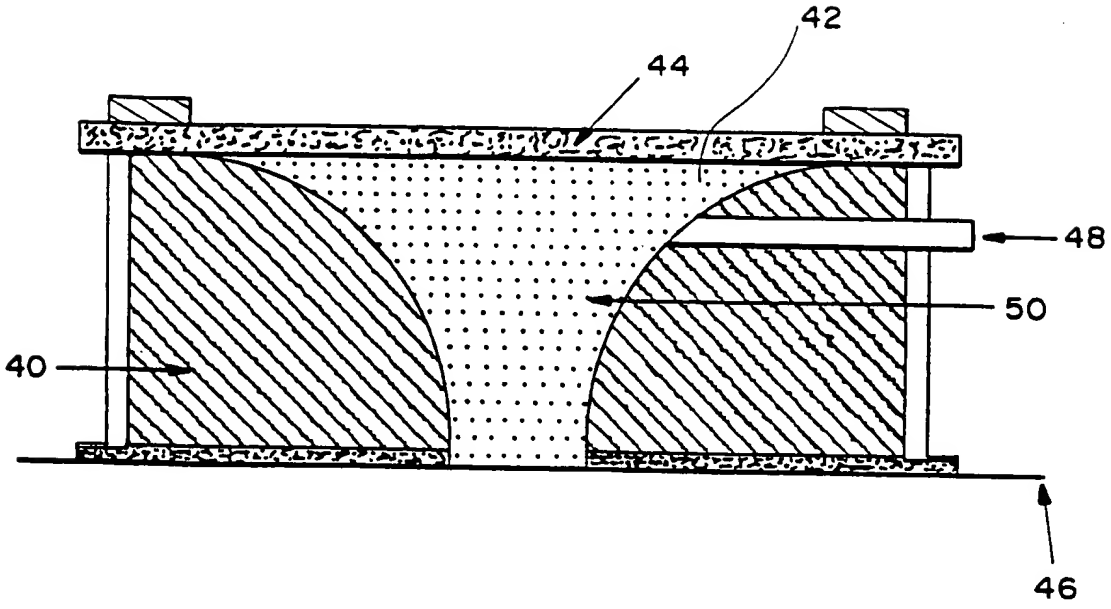


FIG. 3



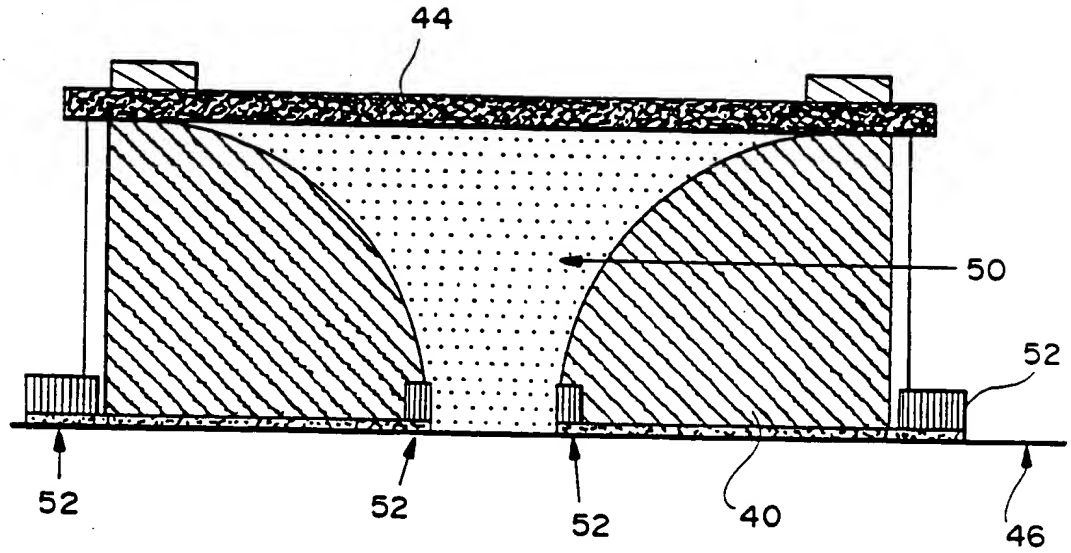


FIG. 4

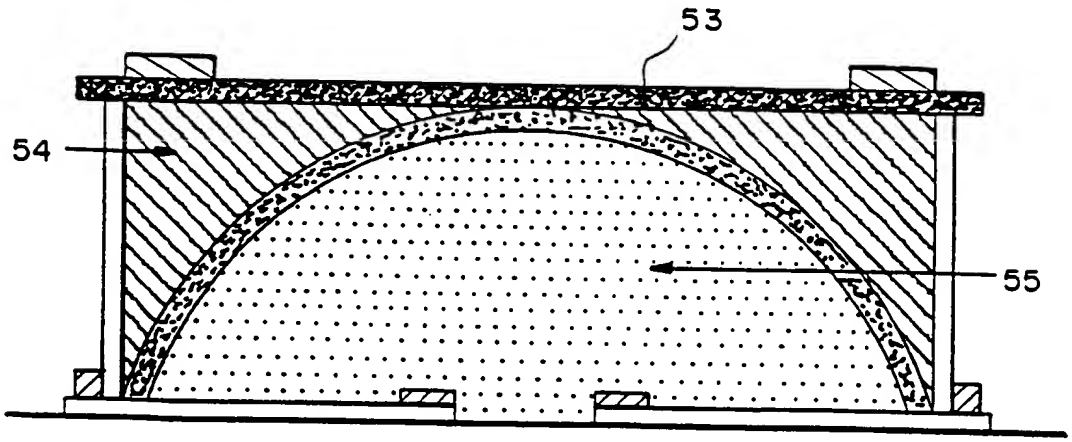
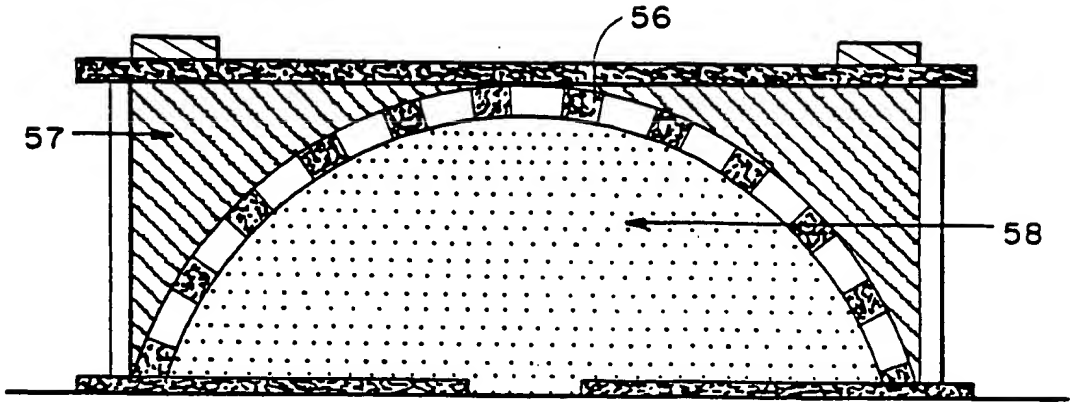


FIG. 5

FIG. 6



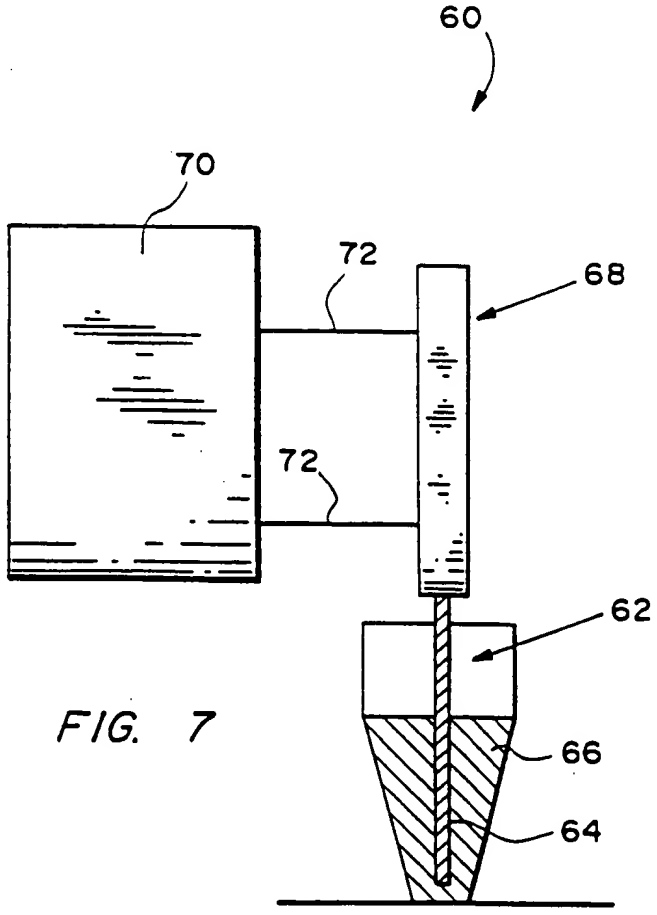


FIG. 7

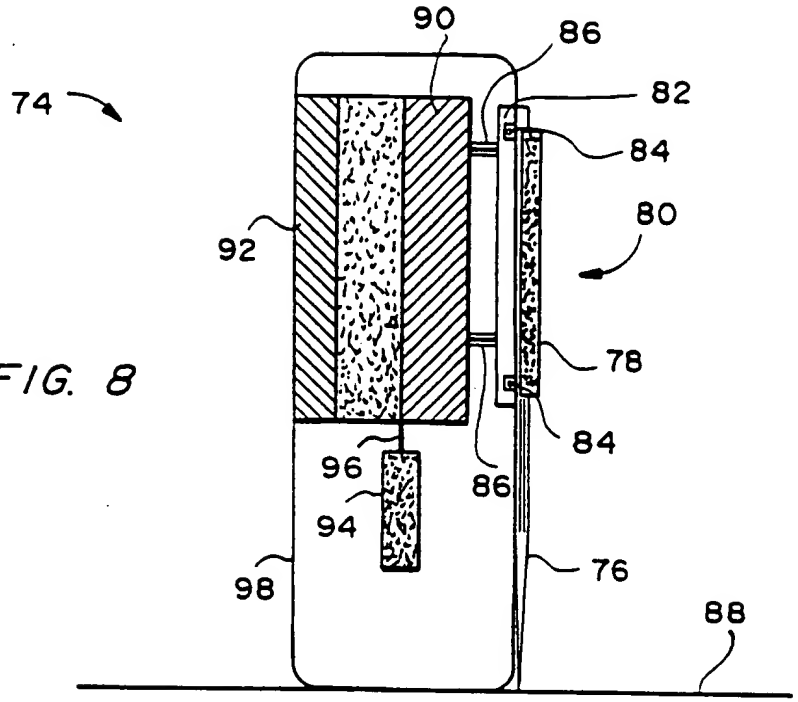

74
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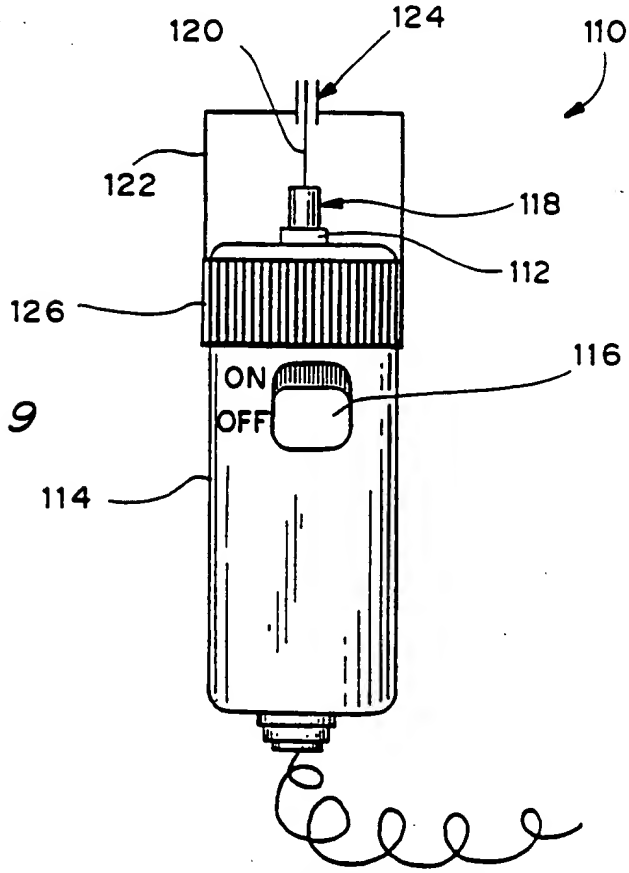
FIG. 8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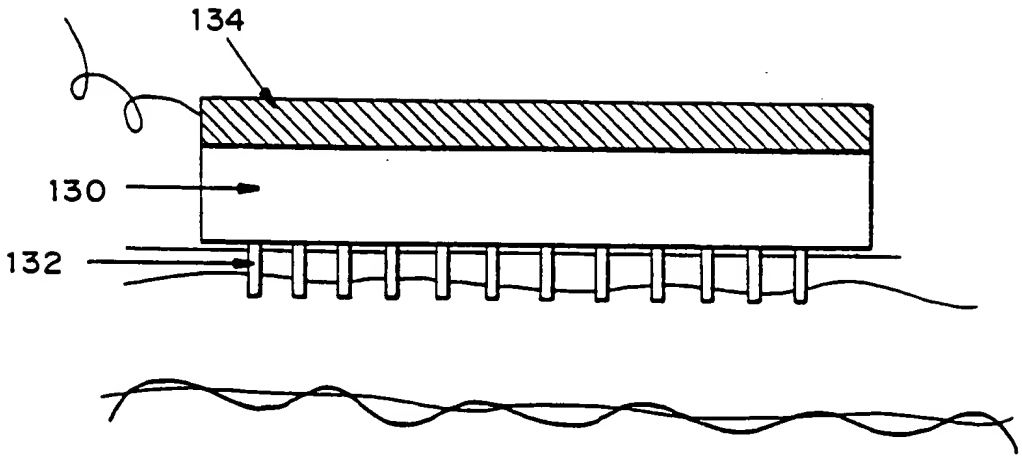
ON
OFF
114

FIG. 9

FIG. 10



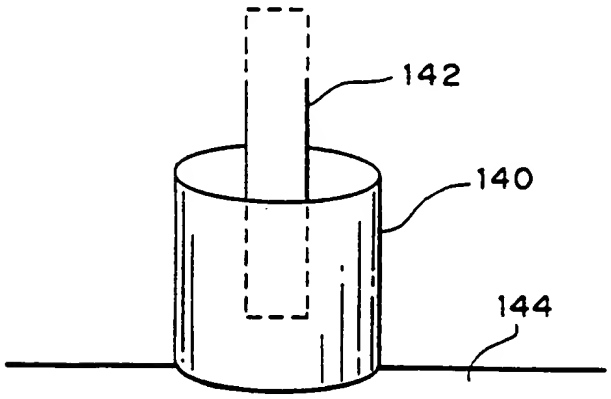


FIG. 11